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LETTERS TO THE EDITOR

RE: "CHILDHOOD CANCER AND POPULATION MIXING"

Population mixing was recently suggested as a possible explanation for the striking cluster of cases of childhood leukemia that occurred in Fallon, Nevada, in 2000–2001 (1). Law et al. (2) sought to test the plausibility of this suggestion by investigating whether population mixing played any part in the production of the disease in a large case-control study of childhood cancer in the United Kingdom. They concluded that it did not and consequently questioned the validity of the hypothesis. It may be doubted, however, whether their findings have any material bearing on the issue, since their definition of population mixing differs greatly from what was meant when population mixing was proposed in the late 1980s as a cause of the disease (3, 4).

The fundamental idea was that in most cases childhood leukemia is a rare response to a common but unidentified infection and that a localized epidemic of this underlying infection might occur, as epidemics of other such diseases have occurred, when a large group of people—many with urban backgrounds and therefore exposed to a wide variety of infections—moves into a sparsely populated area where a substantial proportion of the population has not been so exposed and is therefore susceptible to infection. Studies of large-scale urban-rural mixing in rural areas of the United Kingdom (all associated with population increase and often crowding) during the years 1941–1988, as well as other studies conducted elsewhere, have shown significant excesses of childhood leukemia (5, 6). In exceptional circumstances, it might be possible to detect excesses of the disease from unusual population movements in urban areas (7), but the essence of the concept was the influx of infected persons into a previously sparsely populated area. In contrast, the data of Law et al. (2) were largely derived from the movements of people within and between urban areas as indicated by a single census, without necessarily any marked increase in population. Large numbers of susceptible persons were unlikely to be found in such areas, and consequently the circumstances required for the occurrence of epidemics did not exist. Indeed, there is no indication that any example of rural population mixing comparable to the situations previously studied (5, 6) was covered by Law et al. What is surprising is their chosen approach, given the previous announcement that the case-control study from which they obtained their data was planned in order to investigate childhood leukemia "in rural areas of marked population mixing" (8, p. 1074).

Fallon, Nevada, is a small town in a large desert area near the Fallon naval air base, at which the intake of trainees had been increased just prior to 2000 from 20,000 per year to 50,000 per year—aspects that were not mentioned by Law et al. (2). Under these circumstances, the relevance of population mixing is clear, and it is not surprising that the expert panel which examined the Fallon childhood leukemia cluster identified population mixing as a possible explanation (1). It is notable that this is not the only example of increases in military personnel in rural areas being followed by excesses of childhood leukemia (5, 6).

The overall evidence for an infective basis of childhood leukemia and for a role of unusual rural population mixing is compelling (9). The study by Law et al. (2) does not materially detract from this conclusion or from the plausibility of the concept of population mixing as an explanation for the Fallon cluster.

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In a recent article, Law et al. (1) stated that the findings of their case-control study support the Greaves hypothesis, which postulates an increased risk of childhood acute lymphoblastic leukemia (ALL) from infections delayed

beyond infancy, in contrast to infections experienced in infancy, which would tend to be protective (2). Unfortunately, the authors did not provide data on the most informative group with which to assess protection resulting from early infection: children aged 1–4 years during the study period (1991–1996, though mainly 1992–1994) who were exposed to the highest numbers of recent migrants. Instead, the only results presented for specific age groups, the groups 5–9 and 10–14 years, concerned children who were mainly well past infancy in 1991. From Greaves' hypothesis (2), one would expect that for these children, a high level of exposure to migrants would have represented a source of "delayed" infections and therefore of increased ALL risk. However, Law et al. reported increased risks of ALL in these age groups of 1.92 and 2.06, respectively, among children who were *least* exposed to migrants (1). Contrary to their conclusions, the findings of Law et al. for children aged 5–14 years appear to contradict Greaves' hypothesis.

Particularly since Greaves himself was associated with this study, it is also rather surprising that his hypothesis should now be claimed as predicting protection against ALL from population mixing; previously (2) he stated that it readily accommodates the opposing effects postulated and found by Kinlen (3)—that is, *excesses* of childhood leukemia associated with marked population mixing in rural or isolated areas.

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THE AUTHORS REPLY

We thank Professor Kinlen (1) and Dr. Tucker (2) for their observations on our recently published United Kingdom Childhood Cancer Study (UKCCS) report on childhood cancer and population mixing (3). The investigation was aimed at evaluating the relation between population mixing and childhood leukemia risk in small geographic areas across the United Kingdom. Subjects involved in the UKCCS were not selected on the basis of the leukemia incidence or population density of their region of residence. Furthermore, the census-based method used is reproducible and robust, and the analyses are not affected by participation or recall bias.

We are aware that Professor Kinlen's hypothesis (4) is not applicable to the majority of leukemias diagnosed in children and that it is difficult to test in a national setting (5). In this context, we agree that it is important to focus on extremes of population mixing in sparsely populated areas (1), both within the United Kingdom and elsewhere in the world. With respect to the former, such an investigation will form the basis of an upcoming UKCCS analysis comparing small-area census data of cases with those of controls at birth as well as at diagnosis. The recent acquisition of the birth certificates of all subjects registered in the UKCCS means that we can investigate area characteristics at both of these time points, as well as examine mobility and other changes occurring in between.

Dr. Tucker (2) rightly notes that we did not provide data on the age and diagnostic group most relevant to the delayed infection hypothesis (4). When the analysis was restricted to common acute lymphoblastic leukemia (ALL) diagnosed between the ages of 2 and 5 years, the results were similar to those presented for total ALL (3). For example, for ALL in the lowest category of diversity of migrants, the odds ratio was 1.29 (95 percent confidence interval: 0.79, 2.12) as compared with 1.37 (95 percent confidence interval: 1.00, 1.86) for the totality. The results did not differ when adjustment was made for deprivation and rural status, and there was no evidence of increased risk for areas with a high volume of migrants.

The biologic diversity of childhood leukemias makes it unlikely that there is a solitary cause. It seems clear, however, that research on possible immunologic and infectious etiologies is worth pursuing.

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RE: "RISK ANALYSIS OF ASEPTIC MENINGITIS AFTER MEASLES-MUMPS-RUBELLA VACCINATION IN KOREAN CHILDREN BY USING A CASE-CROSSOVER DESIGN"

Ki et al. (1) used a case-crossover design to evaluate the relative risk of aseptic meningitis after measles-mumps-rubella vaccination. Although their results are broadly in line with those of others on the same topic, the case-crossover